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SENT VIA UNITED PARCEL SERVICE

JUL 16 1999

Dockets Management Branch
Food and Drug Administration
HFA-305, Room 1061
5630 Fishers Lane
Rockville, MD 10852

Dear Sir/Madam:

Re: Docket Number 99D-0674

Reference is made to the FDA Draft Guidance entitled, "INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products", which was published in the Federal Register on April 21, 1999.

AstraZeneca Pharmaceuticals has reviewed this draft document; our comments are attached.

Please do not hesitate to contact me should you require clarification on any of the above comments.

Sincerely,

Robert Castor
Assistant Director
Chemistry, Manufacturing and Controls Group
Drug Regulatory Affairs Department
(302) 886-2594
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RC/CSF/car
Attachment

99D-0674

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Draft Guidance: INDs For Phase 2/3 Studies Of Drugs, Including Specified Therapeutic Biotechnology-Derived Products

AstraZeneca Pharmaceuticals Comments

General Comments:

This guidance is reasonable in terms of requirements for drug substance and drug product. The information requested at phase 2 and phase 3 build on each other such that industry provides a progression of data to the Agency at the end of phase 3. We have pointed out areas of concern where the Agency could provide a clearer definition of the data requirements. This will help industry expedite the process of presenting a data continuum, which ultimately, builds the NDA.

The landscape tabular presentation, with IND section numbering, of the preliminary draft guidance (published December 1997) is preferred since this format allowed easy comparison between the IND phases.

Specific Comments:

Throughout the document, Certificates of Analysis (COAs) are requested to be submitted. Please clarify that it is acceptable to provide batch analysis tables in lieu of signed certificates which are scanned into the document.

Lines 141-142, Phase 2, Drug Substance, Synthesis/Method of Manufacture and Controls:

The rationale and need for providing safety updates on reagent, solvents, etc. is not clear; especially since this information is readily available in the public domain. We suggest omitting this requirement.

Lines 152-153, Phase 2, Drug Substance, Synthesis/Method of Manufacture and Controls and Lines 260-264, Phase 2, Drug Product, Method of Manufacturing, Packaging and Process Controls:

There is disagreement between the drug substance and drug product sections regarding the amount of detail required for equipment and in-process controls in phase 2. Lines 152-153 clearly require that equipment and controls for drug substance be listed, while lines 260-64 say that information does not need to be provided for specific equipment used or for in-process controls employed. More detail is being required for drug substance than for drug product-please clarify the contents of these 2 sections.

Lines 191-192, Phase 2, Drug Substance, Specification and Lines 281-282, Phase 2, Drug Product, Specification:

We suggest rewording these lines from "...complete description of the analytical procedures and supporting validation data should be available on request," to "...analytical procedure and appropriate supporting validation data ...." This would underscore the concept of providing more validation as the method development progresses between phases.

Lines 208-210, Phase 2, Drug Substance, Stability:

Stability indicating analytical procedures may not be finalized for phase 2, but this information will be accumulated as development proceeds through phase 3. Please clarify the requirement outlined in lines 208-210, with reference to phase 2.

Line 220, Phase 2, Drug Substance, Stability:

We suggest editing this line to read, "all available stability data for the clinical material used in the phase 1 study should be provided." This clarifies the degree of the requirement which is to be met at phase 2 studies as opposed to phase 3.

Line 220, Phase 2, Drug Substance, Stability and Line 303, Phase 2, Drug Product, Stability:

These lines imply that industry must do all stability testing on actual batches used in clinical studies. Please clarify-is it acceptable to perform stability on phase 2 batches not used in the clinic, but are otherwise equivalent to the clinical batches?

Line 236, Phase 2, Drug Product, Component/Composition/Batch Formula; Line 295, Phase 2, Drug Product, Container Closure System; Line 462, Phase 3, Drug Product, Components/Composition/Batch Formula, and Line 528, Phase 3, Drug Product, Container/Closure System:

These lines all reference the requirement for container closure systems to be similar to the intended marketed package for drug products delivered by devices (e.g., MDIs, DPIs, and nasal sprays). Please provide more detailed guidance on how to demonstrate "similarity" for device designs. Also, please clarify the differences in requirements for demonstrating similarity between phases 2 and 3.

Lines 245-246, Phase 2, Drug Product, Specification for Components:

We suggest deleting the requirement for analytical procedures and acceptance criteria for non-compendial components at phase 2.

Lines 345-347, Phase 3, Drug Substance, Synthesis/Method of Manufacture and Controls:

We suggest deleting the requirement for providing analytical procedures. AstraZeneca believes this is burdensome for starting materials in a phase 3 IND. Providing this information for a NDA should be sufficient.

Lines 352-354:

The provision for full description of the manufacturing process "may also be needed" is too vague. In critical cases, such as monoclonal antibodies configured in affinity matrices, we suggest that safety related aspects should be discussed and a full description of the manufacturing process should be available on request.

Line 366:

We believe it is unnecessary to include complete descriptions of in-process analytical methods in the list of relevant information for the drug substance. Please revise this requirement to be consistent with line 376, which states that the description of analytical procedures should be "brief."

Lines 367-369:

We suggest that, for specified biotechnology products, that the appropriate validation of the genetic stability be performed.

Lines 398-400, Phase 3, Drug Substance, Specification and Lines 505-508, Phase 3, Drug Product, Specification:

In reference to providing sponsor's standard test procedure numbers, we believe this is unnecessary, given that procedures are often still in the development laboratory. Please revise this requirement for phase 3 drug substance and drug product.

Lines 404-405, Phase 3, Drug Substance, Specification:

We suggest that the stated reference be updated to ICH/USP methods validation guidelines.

Line 409:

We suggest replacing "manufacturing experience" with "levels qualified in safety studies." The amount of "manufacturing experience" will still be low in phase 3. Further the ICH document Q6A, Step 2 indicates that it is "inappropriate to establish acceptance criteria which tightly encompass the batch data at the time of filing."

Lines 409-411:

The requirement for suitable microbial limits for non-sterile products seems new and is not currently required at the NDA stage. Please explain this discrepancy in requirement -- AstraZeneca is opposed to the requirement at the IND phase; we believe that microbial limits should be set only where necessary.

Lines 433-440, Phase 3 Drug Substance, Stability and Lines 537-550; Phase 3 Drug Product, Stability:

The guidance states that the stability methods need to be described in detail; however, in other sections that discuss methods for drug substance and drug product, only a general description is required. This seems inconsistent. Please clarify.

Lines 433-440, Phase 3 Drug Substance, Stability and Lines 537-550; Phase 3 Drug Product, Stability:

We strongly object to the requirement to report "individual data points for each test..." on stability. Only mean results should be required. Reporting all of the individual tests would result in excessively cumbersome data tables and substantially increase the size of the submission. Individual data points are not required for NDAs -- please clarify why the requirement should be greater for phase 3 INDs. In the past, we have provided the individual data points on a computer disk for NDAs if the FDA requested them.

"A summary table of test results" is required for Batch Results. We suggest the same for stability.

Lines 455-462, Phase 3, Drug Product, Components, Composition, and Batch Formula:

The guidance is silent about batch results for drug product. The guidance is specific about providing a summary table for phase 3 batch results for drug substance (lines 413-415). Please clarify the requirement.

Line 518, Phase 3, Drug Product, Specification:

We suggest adding the verbiage contained in lines 286-287 to the end of line 518. The addition reads, "A summary table of test results, analytical data (e.g. chromatogram), and COA for lots of drug product used in clinical studies should be provided."

Lines 581-583 Resources:

Please strengthen the statement in the resources section pertaining to ICH references with the following revision: "although not applicable to IND applications, the International Conference on Harmonization (ICH) documents below can serve as valuable resources in guiding the course of product development."

CSF/car

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